PEGASYS â

(peginterferon alfa-2a)

Alpha interferons, including PEGASYS, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping PEGASYS therapy (see WARNINGS and ADVERSE REACTIONS).

DESCRIPTION

PEGASYS, peginterferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40,000 daltons). The PEG moiety is linked at a single site to the interferon alfa moiety via a stable amide bond to lysine. Peginterferon alfa-2a has an approximate molecular weight of 60,000 daltons. Interferon alfa-2a is produced using recombinant DNA technology in which a cloned human leukocyte interferon gene is inserted into and expressed in *Escherichia coli*.

Each vial contains approximately 1.2 mL of solution to deliver 1.0 mL of drug product. Subcutaneous (SC) administration of 1.0 mL delivers 180 µg of drug product (expressed as the amount of interferon alfa-2a), 8.0 mg sodium chloride, 0.05 mg polysorbate 80, 10.0 mg benzyl alcohol, 2.62 mg sodium acetate trihydrate, and 0.05 mg acetic acid. The solution is colorless to light yellow and the pH is 6.0 ± 0.01.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Interferons bind to specific receptors on the cell surface initiating intracellular signaling via a complex cascade of protein-protein interactions leading to rapid activation of gene transcription. Interferon-stimulated genes modulate many biological effects including the inhibition of viral replication in infected cells, inhibition of cell proliferation, and immunomodulation. The clinical relevance of these in vitro activities is not known.

Peginterferon alfa-2a stimulates the production of effector proteins such as serum neopterin and 2',5'-oligoadenylate synthetase, raises body temperature, and causes reversible decreases in leukocyte and platelet counts. The correlation between the in vitro and in vivo pharmacology and pharmacodynamic and clinical effects is unknown.

Pharmacokinetics

Maximal serum concentrations (C_{max}) occur between 72 to 96 hours post dose, and are sustained for up to 168 hours. The C_{max} and AUC measurements of PEGASYS increase in a dose-related manner. Week 48 mean trough concentrations (16 ng/mL; range 4 to 28) are approximately 2-fold higher than week 1 mean trough concentrations (8 ng/mL; range 0 to 15). Steady-state serum levels are reached within 5 to 8 weeks of once weekly dosing. The peak to trough ratio at week 48 is approximately 2.0.

The mean systemic clearance in healthy subjects given PEGASYS was 94 mL/h, which is approximately 100-fold lower than that for interferon alfa-2a (ROFERON®-A). The mean terminal half-life after SC dosing in patients with chronic hepatitis C was 80 hours (range 50 to 140 hours) compared to 5.1 hours (range 3.7 to 8.5 hours) for ROFERON-A.

PEGASYS administration yielded similar pharmacokinetics in male and female healthy subjects. The AUC was increased from 1295 to 1663 ng·h/mL in subjects older than 62 years taking 180 µg PEGASYS, but peak concentrations were similar (9 vs 10 ng/mL) in those older and younger than 62 years.

In patients with end stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in clearance (see **PRECAUTIONS: Renal Impairment**).

The pharmacokinetics of PEGASYS has not been adequately studied in pediatric patients.

CLINICAL STUDIES

The safety and effectiveness of PEGASYS for the treatment of hepatitis C infection were assessed in three randomized, open-label, active-controlled clinical studies. All patients were adults and had compensated liver disease and detectable hepatitis C virus (HCV), and were previously untreated with interferon. All patients received therapy by SC injection for 48 weeks, and were followed for an additional 24 weeks to assess the durability of response. In studies 1 and 2, approximately 20% of subjects had cirrhosis or transition to cirrhosis. Study 3 was designed to enroll only patients with a histological diagnosis of cirrhosis or transition to cirrhosis.

In study 1 (n=630), patients received either ROFERON-A (interferon alfa-2a) 3 MIU three times/week, PEGASYS 135 µg once each week, or PEGASYS 180 µg once each week. In study 2 (n=526), patients received either ROFERON-A 6 MIU three times/week for 12 weeks followed by 3 MIU three times/week for 36 weeks or PEGASYS 180 µg once each week.

In study 3 (n=269), patients received ROFERON-A 3 MIU three times/week, PEGASYS 90 µg once each week, or PEGASYS 180 µg once each week.

Response to treatment was defined in the protocol as two consecutive undetectable HCV RNA values and normalization of ALT (alanine aminotransferase) at 24 weeks post-treatment (undetectable values must have occurred within 2 weeks of the scheduled visits at weeks 68 and 72 and must have been drawn at least 21 days apart). An exploratory analysis was also conducted in which response to treatment was defined as undetectable HCV RNA and normalization of ALT post-treatment (on or after study week 68). The results of the original and exploratory analysis are provided in Table 1.

In all three studies, treatment with PEGASYS 180 µg resulted in significantly more responding patients compared to treatment with ROFERON-A (see **Table 1**).

In study 1, response to PEGASYS 135 µg was not different from responses to 180 µg. In study 3, response rates with PEGASYS 90 µg were intermediate between PEGASYS 180 µg and ROFERON-A.

Table 1 Sustained Response at Week 72

	Study 1			**Study 2**			**Study 3 (With Cirrhosis)**		
	ROFERON-A 3 MIU (N=207)	**PEGASYS 180 mg (N=208)**	**PEGASYS – ROFERON-A (95% CI)**	**ROFERON-A 6/3 MIU (N=261)**	**PEGASYS 180 mg (N=265)**	**PEGASYS – ROFERON-A (95% CI)**	**ROFERON-A 3 MIU (N=86)**	**PEGASYS 180 mg (N=87)**	**PEGASYS – ROFERON-A (95% CI)**
Protocol:†									
Combined Virological and Biological Sustained Responder (wk 72)	9%	20%	11% (4%, 17%)	15%	28%	13% (6%, 20%)	3%	20%	16% (7%, 25%)
Sustained Virological Response*	9%	23%	13% (7%, 20%)	17%	31%	14% (7%, 22%)	5%	28%	23% (13%, 33%)
Exploratory:†									
Combined Virologic Response and Biological Sustained Responder (wk 72)	11%	24%	13% (6%, 20%)	17%	35%	18% (11%, 25%)	7%	23%	16% (6%, 26%)
Sustained Virological Response*	11%	26%	15% (8%, 23%)	19%	38%	19% (11%, 26%)	8%	30%	22% (11%, 33%)

*COBAS AMPLICOR® HCV Test, version 2.0, is a registered trademark of Roche Molecular Systems, Inc.

† See text for response definition.

Matched pre- and post-treatment liver biopsies were obtained in approximately 70% of patients. Similar modest reductions in inflammation and fibrosis compared to baseline were observed in all treatment groups.

Of patients who did not demonstrate by 12 weeks of PEGASYS 180 µg therapy, either undetectable HCV RNA or at least a 2-log10 drop in HCV

RNA titer from baseline, 2% (3/156) achieved a sustained virological response (see **DOSAGE AND ADMINISTRATION**).

Averaged over study 1, study 2, and study 3, response rates to PEGASYS were 23% among patients with viral genotype 1 and 48% in patients with other viral genotypes.

The treatment response rates were similar in men and women and in non-Caucasians compared to Caucasians. However, the total number of non-Caucasian patients was too small to rule out substantial differences.

INDICATIONS AND USAGE

PEGASYS, peginterferon alfa-2a, is indicated for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not been previously treated with interferon alfa. Patients in whom efficacy was demonstrated included patients with compensated cirrhosis.

CONTRAINDICATIONS

PEGASYS is contraindicated in patients with:

- hypersensitivity to PEGASYS or any of its components
- autoimmune hepatitis
- decompensated hepatic disease prior to or during treatment with PEGASYS

PEGASYS is also contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants which are sometimes fatal.

WARNINGS

General

Patients should be monitored for the following serious conditions, some of which may become life threatening. Patients with persistently severe or worsening signs or symptoms should have their therapy withdrawn (see **BOXED WARNING**).

Neuropsychiatric

Life-threatening neuropsychiatric reactions may manifest in patients receiving therapy with PEGASYS. Depression, suicidal ideation, and suicidal attempt may occur in patients with and without previous psychiatric illness.

PEGASYS should be used with extreme caution in patients who report a history of depression. Neuropsychiatric adverse events observed with alpha interferon treatment include relapse of drug addiction, drug overdose, aggressive behavior, psychoses, hallucinations, bipolar disorders and mania.

Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. Patients should be advised to report any sign or symptom of depression or suicidal ideation to their prescribing physicians. In severe cases, therapy should be stopped immediately and psychiatric intervention instituted (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Bone Marrow Toxicity

PEGASYS suppresses bone marrow function and may result in severe cytopenias. Very rarely alpha interferons may be associated with aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS: Laboratory Tests**).

PEGASYS should be used with caution in patients with baseline neutrophil counts <1500 cells/mm^3, with baseline platelet counts <90,000 cells/mm^3 or baseline hemoglobin <10 g/dL. PEGASYS therapy should be discontinued, at least temporarily, in patients who develop severe decreases in neutrophil and/or platelet counts (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Cardiovascular Disorders

Hypertension, supraventricular arrhythmias, chest pain, and myocardial infarction have been observed in patients treated with PEGASYS.

PEGASYS should be administered with caution to patients with preexisting cardiac disease.

Hypersensitivity

Severe acute hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If such reaction occurs, therapy with PEGASYS should be discontinued and appropriate medical therapy immediately instituted.

Endocrine Disorders

PEGASYS causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia, hypoglycemia, and diabetes mellitus have been observed to develop in patients treated with PEGASYS. Patients with these conditions at baseline who cannot be effectively treated by medication should not begin PEGASYS therapy. Patients who develop these conditions during treatment and cannot be controlled with medication may require discontinuation of PEGASYS therapy.

Autoimmune Disorders

Development or exacerbation of autoimmune disorders including myositis, hepatitis ITP, psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis,

and systemic lupus erythematosus have been reported in patients receiving alpha interferon. PEGASYS should be used with caution in patients with autoimmune disorders.

Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by PEGASYS or alpha interferon therapy. Patients who develop persistent or unexplained pulmonary infiltrates or pulmonary function impairment should discontinue treatment with PEGASYS.

Colitis

Hemorrhagic/ischemic colitis, sometimes fatal, has been observed within 12 weeks of starting alpha interferon treatment. Abdominal pain, bloody diarrhea, and fever are the typical manifestations of colitis. PEGASYS should be discontinued immediately if these symptoms develop. The colitis usually resolves within 1 to 3 weeks of discontinuation of alpha interferon. Ulcerative colitis has also been observed in patients treated with alpha interferon.

Pancreatitis

Pancreatitis, sometimes fatal, has occurred during alpha interferon treatment. PEGASYS should be suspended if symptoms or signs suggestive of pancreatitis are observed. PEGASYS should be discontinued in patients diagnosed with pancreatitis.

Ophthalmologic Disorders

Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema are induced or aggravated by treatment with PEGASYS or other alpha interferons. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (eg, diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. PEGASYS treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

PRECAUTIONS

General

- The safety and efficacy of PEGASYS have not been established in patients who have failed other alpha interferon treatments.
- The safety and efficacy of PEGASYS for the treatment of hepatitis C in liver or other organ transplant recipients have not been established.

- The safety and efficacy of PEGASYS for the treatment of patients with HCV co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) have not been established.

Renal Impairment

A 25% to 45% higher exposure to PEGASYS is seen in subjects undergoing hemodialysis. In patients with impaired renal function, signs and symptoms of interferon toxicity should be closely monitored. Doses of PEGASYS should be adjusted accordingly. PEGASYS should be used with caution in patients with creatinine clearance <50 mL/min (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Information for Patients

Patients receiving PEGASYS should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the PEGASYS Medication Guide.

Patients who develop dizziness, confusion, somnolence, and fatigue should be cautioned to avoid driving or operating machinery.

If home use is prescribed, a puncture-resistant container for the disposal of used needles and syringes should be supplied to the patients. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of any needles and syringes. The full container should be disposed of according to the directions provided by the physician (see enclosed **MEDICATION GUIDE**).

Laboratory Tests

Before beginning PEGASYS therapy, standard hematological and biochemical laboratory tests are recommended for all patients.

After initiation of therapy, hematological tests should be performed at 2 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy. In the clinical studies, the CBC (including hemoglobin level and white blood cell [WBC] and platelet counts) and chemistries (including liver function tests and uric acid) were measured at 1, 2, 4, 6, and 8, and then every 4 weeks, or more frequently if abnormalities were found. Thyroid stimulating hormone (TSH) was measured every 12 weeks.

The entrance criteria used for the clinical studies of PEGASYS may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count ≥90,000 cells/mm^3 (as low as 75,000 cells/mm^3 in patients with cirrhosis or transition to cirrhosis)
- Absolute neutrophil count (ANC) ≥1500 cells/mm^3
- Serum creatinine concentration <1.5 x upper limit of normal

- TSH and T_4 within normal limits or adequately controlled thyroid function

PEGASYS treatment was associated with decreases in WBC, ANC and platelet counts often starting within the first 2 weeks of treatment (see **ADVERSE REACTIONS**). Dose reduction is recommended in patients with hematologic abnormalities (see **DOSAGE AND ADMINISTRATION: Dose Modifications**). In clinical trials with PEGASYS, the hematologic abnormalities were reversible upon dose reduction or cessation of therapy.

While fever may be associated with the flu-like syndrome reported commonly during PEGASYS therapy, other causes of persistent fever must be ruled out, particularly in patients with neutropenia.

Transient elevations in ALT (2-fold to 5-fold above baseline) were observed in some patients receiving PEGASYS, including patients with virologic response. Transient elevations were not associated with deterioration of other liver function tests. However, when the increase in ALT levels is progressive despite dose reduction or is accompanied by increased bilirubin, therapy should be discontinued (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Drug Interactions

Treatment with PEGASYS once weekly for 4 weeks in healthy subjects was associated with an inhibition of P450 1A2 and a 25% increase in theophylline AUC. Theophylline serum levels should be monitored and appropriate dose adjustments considered for patients given both theophylline and PEGASYS (see **PRECAUTIONS**). There was no effect on the pharmacokinetics of representative drugs metabolized by CYP 2C9, CYP 2C19, CYP 2D6 or CYP 3A4.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

PEGASYS has not been tested for its carcinogenic potential.

Mutagenesis

PEGASYS did not cause DNA damage when tested in the Ames bacterial mutagenicity assay and in the in vitro chromosomal aberration assay in human lymphocytes, either in the presence or absence of metabolic activation.

Impairment of Fertility

PEGASYS may impair fertility. Prolonged menstrual cycles and/or amenorrhea were observed in female cynomolgus monkeys given SC injections of 600 µg/kg/dose (7200 $\mu g/m^2$/dose) of PEGASYS every other day for one month, at approximately 180 times the recommended weekly human dose for a 60 kg person (based on body surface area). Menstrual cycle

irregularities were accompanied by both a decrease and delay in the peak 17β-estradiol and progesterone levels following administration of PEGASYS to female monkeys. A return to normal menstrual rhythm followed cessation of treatment. Every other day dosing with 100 µg/kg (1200 µg/m^2) PEGASYS (equivalent to approximately 30 times the recommended human dose) had no effects on cycle duration or reproductive hormone status.

The effects of PEGASYS on male fertility have not been studied. However, no adverse effects on fertility were observed in male Rhesus monkeys treated with non-pegylated interferon alfa-2a for 5 months at doses up to 25 x 10^6 IU/kg/day.

Pregnancy

Pregnancy Category C

PEGASYS has not been studied for its teratogenic effect. Non-pegylated interferon alfa-2a treatment of pregnant Rhesus monkeys at approximately 20 to 500 times the human weekly dose resulted in a statistically significant increase in abortions. No teratogenic effects were seen in the offspring delivered at term. PEGASYS should be assumed to also have abortifacient potential. There are no adequate and well-controlled studies of PEGASYS in pregnant women. PEGASYS is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. PEGASYS is recommended for use in women of childbearing potential only when they are using effective contraception during therapy.

Nursing Mothers

It is not known whether PEGASYS or its components are excreted in human milk. The effect of orally ingested PEGASYS from breast milk on the nursing infant has not been evaluated. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue the treatment.

Pediatric Use

The safety and effectiveness of PEGASYS in children below the age of 18 years have not been established.

PEGASYS contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal.

Geriatric Use

Clinical studies of PEGASYS did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Adverse reactions related to alpha interferons, such as CNS, cardiac, and systemic (eg, flu-like) effects may be more severe in the elderly and

caution should be exercised in the use of PEGASYS in this population. This drug is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

ADVERSE REACTIONS

PEGASYS causes a broad variety of serious adverse reactions (see **BOXED WARNING** and **WARNINGS**). In all studies, one or more serious adverse reactions occurred in 9% of patients receiving PEGASYS. Nearly all patients in clinical trials experienced one or more adverse events. The most commonly reported adverse reactions were psychiatric reactions, including depression, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache and rigors. The most common reason for dose modification or withdrawal from studies was hematologic abnormalities.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug. Also, the adverse event rates listed here may not predict the rates observed in a broader patient population in clinical practice. More than 1000 patients have been treated with PEGASYS in clinical trials. Table 2 shows those adverse reactions occurring in ≥5% of patients receiving PEGASYS 180 µg (n=559) in clinical trials. The population encompassed an age range of 18 to 76. Seventy percent of the patients were male and 86% were Caucasian.

Table 2 Adverse Reactions Occurring in ≥ 5% of Patients in Hepatitis C Clinical Trials (Pooled Studies 1, 2, and 3)

Body System/Adverse Events	PEGASYS 180 mg N = 559 (%)	ROFERON-A* N = 554 (%)
Gastrointestinal		
Nausea	23	30
Diarrhea	16	16
Abdominal pain	15	15
Nausea and vomiting	5	8
Dry mouth	6	3
General		
Fatigue	50	50
Pyrexia	36	41
Rigors	32	42
Injection-site reaction	22	18
Pain	11	12
Asthenia	5	6
Hematologic		
Neutropenia	21	8
Thrombocytopenia	5	2
Metabolism and Nutrition		
Anorexia	17	17
Musculoskeletal, Connective Tissue and Bone		
Myalgia	37	38
Arthralgia	28	29
Back pain	9	10
Neurological		
Headache	54	58
Insomnia	19	23
Dizziness	16	12
Concentration impairment	8	10
Memory impairment	5	4
Psychiatric		
Depression	18	19
Irritability	13	17
Anxiety	6	5
Depressed mood	1	5

Body System/Adverse Events	PEGASYS 180 mg N = 559 (%)	ROFERON-A* N = 554 (%)
Skin and Subcutaneous Tissue		
Alopecia	23	30
Pruritus	12	8
Sweating increased	6	7
Dermatitis	8	3
Rash	5	4

*Either 3 MIU or 6/3 MIU of ROFERON-A.

Serious adverse events included the following: substance overdose, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, suicidal ideation, suicide, diabetes mellitus, autoimmune phenomena, peripheral neuropathy, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, endocarditis, pneumonia, interstitial pneumonitis, pulmonary embolism, coma, myositis, and cerebral hemorrhage. Each of the above individual events occurred at a frequency of ≤1%.

Laboratory Test Values

Hematology

Treatment with PEGASYS 180 µg was associated with decreases in total WBC, ANC and platelet counts, which generally improved with dosage modification and returned to pre-treatment levels within 4 to 8 weeks upon cessation of therapy (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Approximately 4% of patients had transient decreases in ANC to levels below 500 cells/mm^3 at some time during therapy. PEGASYS treatment was also associated with decreases in values for platelet counts. Approximately 5% of patients had decreases in platelet counts to levels below 50,000 cells/mm^3.

Although treatment with PEGASYS 180 µg was associated with small gradual decreases in hemoglobin and hematocrit, less than 1% of all patients, including those with cirrhosis, required dose modification for anemia.

Thyroid Function

PEGASYS treatment was associated with the development of abnormalities in thyroid laboratory values, some with associated clinical manifestations. The rates of clinically relevant hypothyroidism or hyperthyroidism (requiring treatment, dose modification or discontinuation) were 4% and 1%, respectively. Among the patients who developed new onset thyroid abnormalities during PEGASYS treatment, approximately half still had abnormalities during the follow-up period (see **PRECAUTIONS: Laboratory Tests**).

Immunogenicity

Two percent of patients (8/409) receiving PEGASYS developed low-titer neutralizing antibodies (using an assay of a sensitivity of 100 INU/mL). Six percent (24/409) of patients treated with PEGASYS developed binding antibodies to interferon alfa-2a, as assessed by an ELISA assay.

The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The percentage of patients whose test results were considered positive for antibodies is highly dependent on the sensitivity and specificity of the assays.

Additionally the observed incidence of antibody positivity in these assays may be influenced by several factors including sample timing and handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PEGASYS with the incidence of antibodies to these products may be misleading.

OVERDOSAGE

There is limited experience with overdosage. The maximum dose received by any patient was 7 times the intended dose of PEGASYS (180 µg/day for 7 days). There were no serious reactions attributed to overdosages. Weekly doses of up to 630 µg have been administered to patients with cancer. Dose-limiting toxicities were fatigue, elevated liver enzymes, neutropenia, and thrombocytopenia. There is no specific antidote for PEGASYS. Hemodialysis and peritoneal dialysis are not effective.

DOSAGE AND ADMINISTRATION

The recommended dose of PEGASYS is 180 µg (1.0 mL) once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

There are no safety and efficacy data on treatment for longer than 48 weeks. Consideration should be given to discontinuing therapy after week 12 virological results are available if the patient has failed to demonstrate a response (see **CLINICAL STUDIES**).

A patient should self-inject PEGASYS only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and training in proper injection technique has been provided to him/her (see illustrated **MEDICATION GUIDE** for instructions).

PEGASYS should be inspected visually for particulate matter and discoloration before administration, and not used if particulate matter is visible or product is discolored. Vials with particulate matter or discoloration should be returned to the pharmacist.

Dose Modifications

General

When dose modification is required for moderate to severe adverse reactions (clinical and/or laboratory), initial dose reduction to 135 µg (0.75 mL) is generally adequate. However, in some cases, dose reduction to 90 µg (0.5 mL) may be needed. Following improvement of the adverse reaction, re-escalation of the dose may be considered (see **WARNINGS, PRECAUTIONS**, and **ADVERSE REACTIONS**).

Hematological

Dose reduction to 135 µg PEGASYS is recommended if the neutrophil count is less than 750 cells/mm^3. For patients with ANC values below 500 cells/mm^3, treatment should be suspended until ANC values return to more than 1000 cells/mm^3. Therapy should initially be reinstituted at 90 µg PEGASYS, and the neutrophil count monitored.

Dose reduction to 90 µg PEGASYS is recommended if the platelet count is less than 50,000 cells/mm^3. Cessation of therapy is recommended when platelet count is below 25,000 cells/mm^3.

Renal Function

In patients with end-stage renal disease requiring hemodialysis, dose reduction to 135 µg PEGASYS is recommended. Signs and symptoms of interferon toxicity should be closely monitored.

Liver Function

In patients with progressive ALT increases above baseline values, the dose of PEGASYS should be reduced to 90 µg. If ALT increases are progressive despite dose reduction or accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be immediately discontinued.

HOW SUPPLIED

Single Dose Vial

Each PEGASYS (peginterferon alfa-2a) 180 µg single use, clear glass vial provides 1.0 mL containing 180 µg peginterferon alfa-2a for SC injection. Each package contains 1 vial (NDC 0004-0350-09).

Storage

Store in the refrigerator at 36° to 46°F (2° to 8°C). Do not freeze or shake. Protect from light. Vials are for single use only. Discard any unused portion.

Rx only

Pharmaceuticals

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